UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/579,738	05/26/00	VALLERA	D 11983-004001

HM22/0914

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EXAMINER	
SORRELL,E	
ART UNIT --	PAPER NUMBER
1633	3

DATE MAILED: 09/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/579,738	VALLERA ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 C.F.R. □ 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 C.F.R. □□ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-34, 36, 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase " significant binding". One of skill in the art would not know how to interpret what exactly is meant by significant unless defined more precisely.

Claim 23 recites the phrase "said encoding sequence, a mammalian signal sequence". It is not clear if applicant intends the following: "----said vector further

comprising, 5' of the 5' end of said encoding sequence, wherein said encoding sequence is a mammalian signal sequence".

Claims that depend from the rejected claims are also rejected for the same reasons.

4. Claim 34 recites the limitation "said cell population of claim 20". There is insufficient antecedent basis for this limitation in the claim. Claim 20 is directed to a targeting cell. Appropriate correction is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling for** (1) a targeting cell comprising a retroviral vector comprising a nucleic acid sequence encoding a fusion protein comprising (a) a targeting domain such as IL4 and (b) a toxic domain such as DT390, or PE and (2) treatment of myeloid leukemia by the administration of IL-4DT390, **does not** reasonably provide enablement for any targeting cell comprising any vector encoding a fusion protein that comprises any targeting domain (or functional fragment) and any toxic domain (or functional fragment) for the treatment of any pathogenic cell disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to the construction of any vector comprising sequences encoding an affinity pair or fusion protein, wherein first member comprises a targeting domain and the second member comprises a toxic molecule transfected into a targeting cell. The invention is directed to targeting cells which have affinity for a pathogenic cell wherein the pathogenic cell is any cancer cell, or a cell associated with an autoimmune disease or a cell infected with a microorganism. The claims are also directed to a method of treating a subject with any of the aforementioned pathogenic cell diseases by the administration of cells comprising a retroviral vector comprising sequences encoding an affinity pair or fusion protein, wherein first member comprises any targeting domain and the second member comprises any toxic molecule. The claims also encompass a method for treating a subject with a pathogenic cell disease, such as any cancer, any autoimmune disease or any infection involving any microorganism by the administration of any vector comprising nucleotide sequences encoding the affinity pair or fusion protein referred to above.

The state of the art that encompasses the invention falls into the realm of both *in vivo* and *ex vivo* gene therapy. The state of the art in gene therapy is still in its infancy and is highly unpredictable. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be

advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Retroviral vectors have been used to transfer therapeutic genes ex vivo in clinical trials and the proportion of genetically marked cells recovered from recipients have been observed from several weeks upto 36 months after administration. (See page 405, col. 3, para. 3). He concluded by stating that the results of human gene transfer trials

have been plagued by inconsistency and that the ideal vector for these transfers is conceptually impractical because the human applications are broad and that the ideal vector is different for each application. *(Science Vol. 270, 20 oct 1995, Crystal, pag. 404-410.*

Being a new field the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and induce a therapeutic response across the board. Hence the specification requires detailed methods for preparation of the therapeutic compositions comprising the vectors claimed with specific dosages for specific therapies as claimed by the inventions. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

The claims of the instant invention are unduly broad as they encompass *any target cell* that comprises *any vector* encoding *any targeting domain* and *any toxic domain*. The specification however contains prophetic statements that this modified vector comprising promoters etc as listed in Table 1, page 27-31 of specification for specified purposes without undue experimentation. Therefore, the claims encompass the construction and administration of any and all cells that have been transfected with any vector comprising the components as claimed in the instant invention for the treatment of any cancer as listed in claim 12, or any autoimmune disease or any cell infected with any microorganism. The claims also encompass the construction of any

and all vectors comprising any and all targeting domains that encode the first member of a fusion protein and any and all toxic domains that encode the second member of the fusion protein. The specification defines targeting domains as any cytokine and a toxic domain as any polypeptide that mediates a toxic effect. The specification clearly states that a requirement of practicing the invention is that the targeting domain is any polypeptide that has a significant binding affinity for a molecule on a target cell such as a tumor cell or cell infected or cell that is to be destroyed. Additionally the specification states that the targeting domain of the fusion protein will have a low binding affinity for the entire targeting cell.

The specification teaches the construction of a 1,626 base pair construct comprising the IL-4 domain and the DT390 domain of the diptheria toxin, (sigIL-4DT390) ligated into the mammalian expression vector pcDNA3. The specification also supports the construction of a retroviral vector LNCX in which a gene fragment encoding hNGFR was transduced into a mammalian cell line and expressed NGFR on its surface. The specification teaches *in vivo* examples wherein C57BL/6 mice previously administered C1498 cells (myeoloid leukemia cells) and showing tumor growth, to which the T15, ($CD8^+$ cytotoxic T cell line) comprising a retroviral vector encoding sigIL-4DT390 was administered. Tumor shrinkage was shown by applicants, which indicates that the administered retrovirus recognized the tumor and secreted the immunotoxin, resulting in decrease of the tumor growth. The specification also teaches the construction of a retrovirus comprising sigIL-4 spliced to a coding

sequence encoding the truncated Pseudomonas exotoxin (PE) and cloned into LNCX. The expression of the PE coding sequences in NIH.3T3 cells were also verified.

The specification does not have any guidance as to what targeting ligands one is to use for the breadth of the diseases or target cells claimed. For instance claims 5 and 9 list numerous cytokines used as the first member of the fusion protein and claims 12, 13 list the targeting pathogenic cells. However, the specification does not teach what targeting ligands are to be used with what pathogenic cell. Additionally the specification gave no guidance as to how one is to select for targeting cells so as to prevent the normal cells from being killed while only killing the cells that are being targeted, such as cancer cells. The site of administration was also not taught with regards to all the targeting cells claimed as one would not administer such constructs systemically as the targeting cells would not be able to locate the targeted site without circulating throughout the body.

Therefore, in view of the lack of guidance in the specification with regards to the broad claims as stated above, state of the art, the amount of experimentation required of one of skill in the art will be undue due to the lack of predictability as discussed above.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of vector construction comprising sequences encoding fusion proteins as claimed and for gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, one of skill in the art could not make and use the invention without undue experimentation

7. Claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For one of skill in the art to practice the instant invention one will require the description of nucleic acid sequences that encode all fusion proteins that comprise a targeting domain and a toxic domain and fusion proteins encoding a functional fragment of the targeting domain and a functional fragment of the toxic domain that will fulfill the function as required of the invention in that it will provide the target cell comprising the vector with binding affinity for a specific pathogenic cell.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification provides adequate written description for the claimed invention (methods and products) only with regard to sigIL-4DT390 wherein N-terminal IL-4 was separated from the DT390 domain by a flexible linker with the amino acid sequence EASGGPE (SEQ. ID. NO: 3), the specification fails to describe the other species within the genus of fusion proteins, other than sigIL-4DT390, and sigIL-4PE encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date May/26/99. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments sequences encoding of any and all fusion proteins other than those specifically described, lack a written description. The specification fails to describe what critical elements such as the linker sequences that connect the first member of the affinity pair to the second other than the linker sequence encoded by SEQ. ID. 3 that fall into this genus so as to be constructed and used as claimed, and it was unknown as of Applicants' effective filing date that any of these fusion proteins would have the properties of binding affinity to a pathogenic cell. The skilled artisan cannot envision the detailed chemical structure of all of the

encompassed fusion protein elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the described fusion proteins sigIL-4DT390 and sigIL-4PE, meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 38-41, 43 rejected under 35 U.S.C. 102(b) as being by anticipated by Chan, Chuang-Huang et al. (Blood, Vol. 86. No. 7, 1995, pages 2732-2740).

Chan et al. teach the cytokine fusion toxins wherein the mGM-CSF gene is spliced to a truncated form of diptheria toxin (DT 390) coding for a molecule that retained full enzymatic activity and also taught the construction of a hybrid gene and plasmid. They also taught fusion toxins that specifically target DT to cytokine receptors including interleukin -2, IL-4, IL-6 and G-CSF receptors. They teach mouse cell lines transfected with the plasmid construct comprising the aforesaid components and measured the response. (See Table 2, page 2737).

Therefore, all the limitations encompassed by the claims were anticipated by Chan.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-33, 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan, Chuang-Huang et al. (Blood, Vol. 86. No. 7, 1995, pages 2732-2740 and Blood Vol 88, No. 4 Aug. 15, 1996, pages 1445-1456) in view of Yang, An-Gang (Nature Biotechnology, Vol. 15 , 1997, pages 46-51) and further in view of Chen, Si.,-Yi.(Nature vo. 385, Jan. 1997).

Chan et al. (Blood 86) teach the cytokine fusion toxins wherein the mGM-CSF gene is spliced to a truncated form of diptheria toxin (DT 390) coding for a molecule that retained full enzymatic activity and also taught the construction of a hybrid gene and plasmid. They also taught fusion toxins that specifically target DT to cytokine receptors including interleukin -2, IL-4, IL-6 and G-CSF receptors.. Chan et al. (Blood, Vol. 88) also taught that myeloid leukemias express the IL-3 receptor and therefore they studied the fusion immunotoxin as a potential antileukemia drug consisting of IL3, they studied the mIL-3 gene spliced to a truncated form of the diptheria toxin (DT390).

Chan et al. did not teach nucleotide sequences that encode fusion toxins comprising a toxin such as Pseudomonas exotoxin A (PE) and an antibody or the construction of anti-HIV-1/toxin fusion protein or the generation of cells comprising a toxic molecule that might have applications for the treatment of viral infections.

Chen et al. teach the construction of a plasmid construct encoding PE and a monoclonal antibody with high-affinity binding to the extracellular domain of HER-2 overexpressed on certain human tumors including breast cancer. Chen also taught the generation of retroviral vectors comprising the aforementioned genes. (See Fig. 1 and summary).

Yang et al. teach the construction of recombinant anti-HIV-1 toxin fusion proteins and the generation of a new class of potent antigen-specific killer cells which may have applications in the treatment of viral infection. They also taught recombinant retroviral shuttle vectors encoding the glycoprotein gp120.

Therefore it would have been *prima facie* obvious at the time the invention was made to combine the teachings of Chan, Chen and Yang resulting in the instant application.

Therefore one of ordinary skill in the art would have been motivated to combine the teachings of Chan, Chen and Yang to construct vectors because of their potential application for the *treatment of varied cancers and viral infections and autoimmune diseases.* One of ordinary skill in the art would have reasonably expected success in constructing viral vectors 1comprising a cytokine and the DT290 toxin or PE toxin which would not require undue experimentation.

Therefore, claims 1-33, 36, 37 are rejected as being obvious.

Conclusion

12. Claims 1-43 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eleanor Sorbello whose telephone number is 703-308-6043. The examiner can normally be reached on M-F: 6.30AM-3.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3230 for regular communications and 703-305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

September 10, 2001

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Notice to Comply	Application No. 09/579,738	Applicant(s) Vallera
	Examiner Sorbello	Art Unit 1633

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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